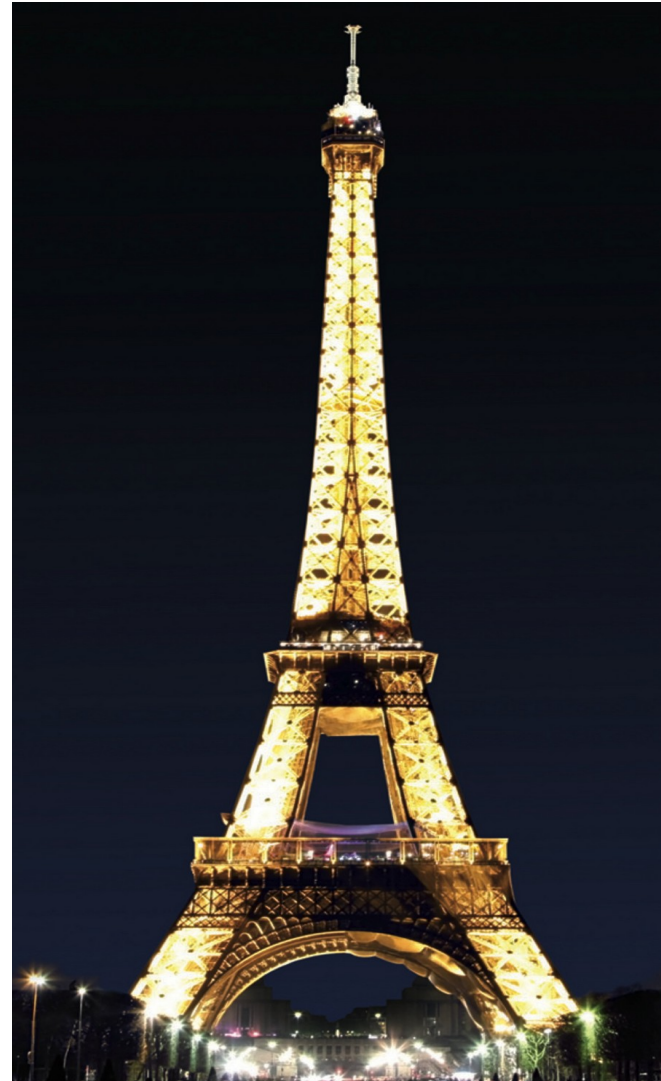


# NASH: Optimal Management

**Dr Raluca Pais**

Institute of Cardiometabolisme and Nutrition (ICAN)

Hôpital Pitie Salpetrière, Paris

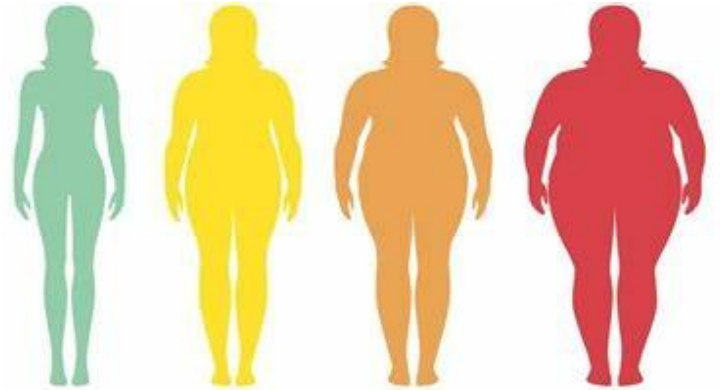


57 years old female

First addressed by the nutritionist for altered LFT  
( $>2.5$  N ) and high ferritin

Morbidly obese: **BMI - 47.83 kg/m<sup>2</sup>** (W = 133kg, T - 167 cm)

20 years 26 years 37 years 57 years



## MEDICAL HISTORY

- ✓ Arterial hypertension since 2000
- ✓ T2DM - since 2010; no macro/microvascular complication
- ✓ OSA; AHI = 16/h
- ✓ Clinical significant knee osteoarthritis
- ✓ Hypothyroidia

Alcohol : 10 g/day (wine)

Former tobacco use (10 PY)

Retired

Low physical activity level

## BLOOD TESTS RESULTS

- ✓ LFT: AST = 48 IU/L, ALT = 56 IU/L, GGT = 82 IU/L,
- ✓ FG = 7.2 mmol/l; HbA1C = 8%
- ✓ Creatinin = 62  $\mu$ mol/l.
- ✓ Albumin = 36g/l
- ✓ Ferritine = 441  $\mu$ g/l; Sat Coef = 34%
- ✓ LDL = 1.46 g/L, CT = 2.25; TG = 2.09; HDL = 0.37

## NON INVASIVE EVALUATION OF LIVER FIBROSIS

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST Level (U/L)}}{\text{Platelet Count (10}^9\text{/L)} \times \sqrt{\text{ALT (U/L)}}} = 1.83$$

## TREATMENT :

METFORMIN 1000 mg,  
IRBESARTAN/HCT 150/12.5 mg,  
LTHYROXIN 75  $\mu$ g

**LIVER ULTRASOUND** – Steatosis, no signs of PHT

## WHAT TEST WOULD YOU FURTHER PERFORM TO ASSESS THE SEVERITY OF THE LIVER DAMAGE?

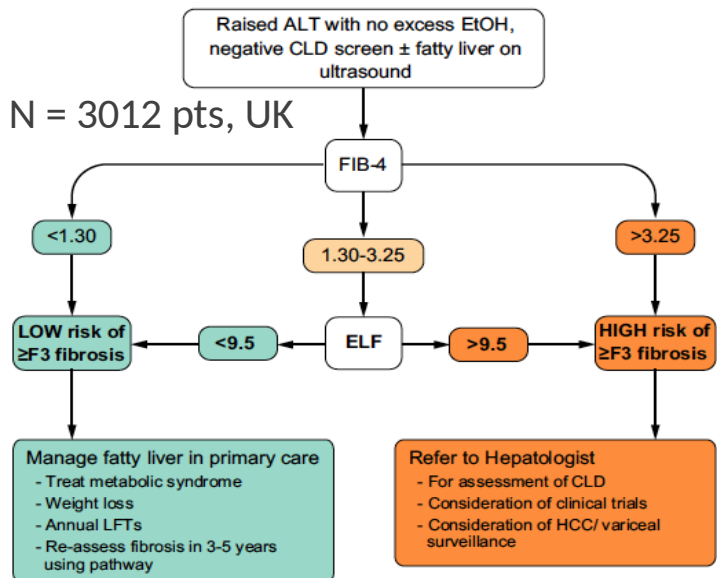


- A 2<sup>nd</sup> simple blood tests (APRI, BARD, NFS Fibrosis score)
- Second line blood tests (Fibrotest, FibroMeter, ELF)
- Transient Elastography (TE)
- Combination of second line blood test and TE

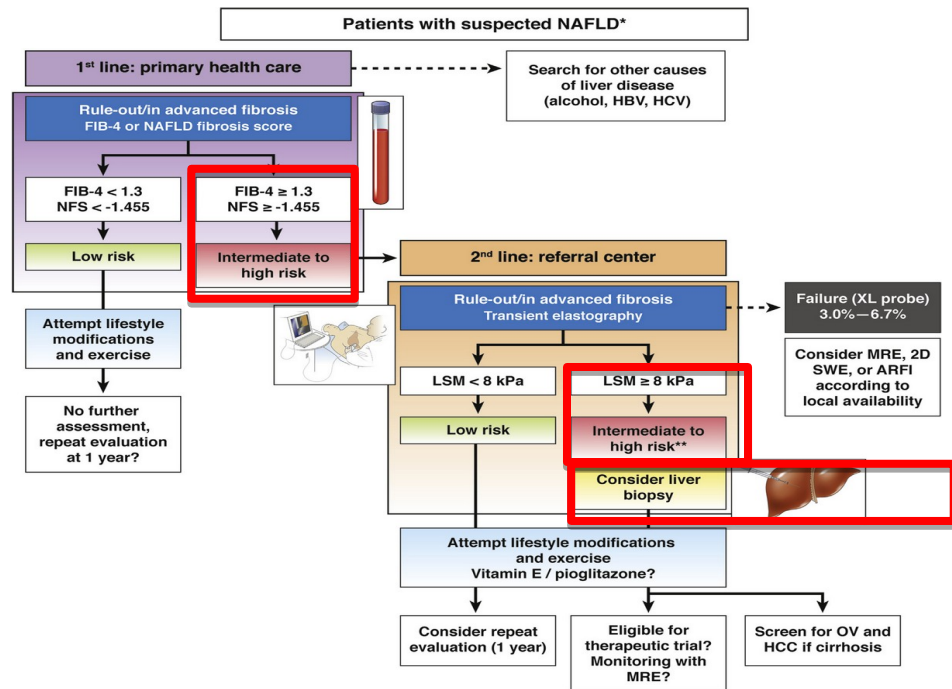


# First-line diagnostic tests in primary care settings

- Reduce unnecessary referral from primary to secondary care
- Detect significant fibrosis and cirrhosis



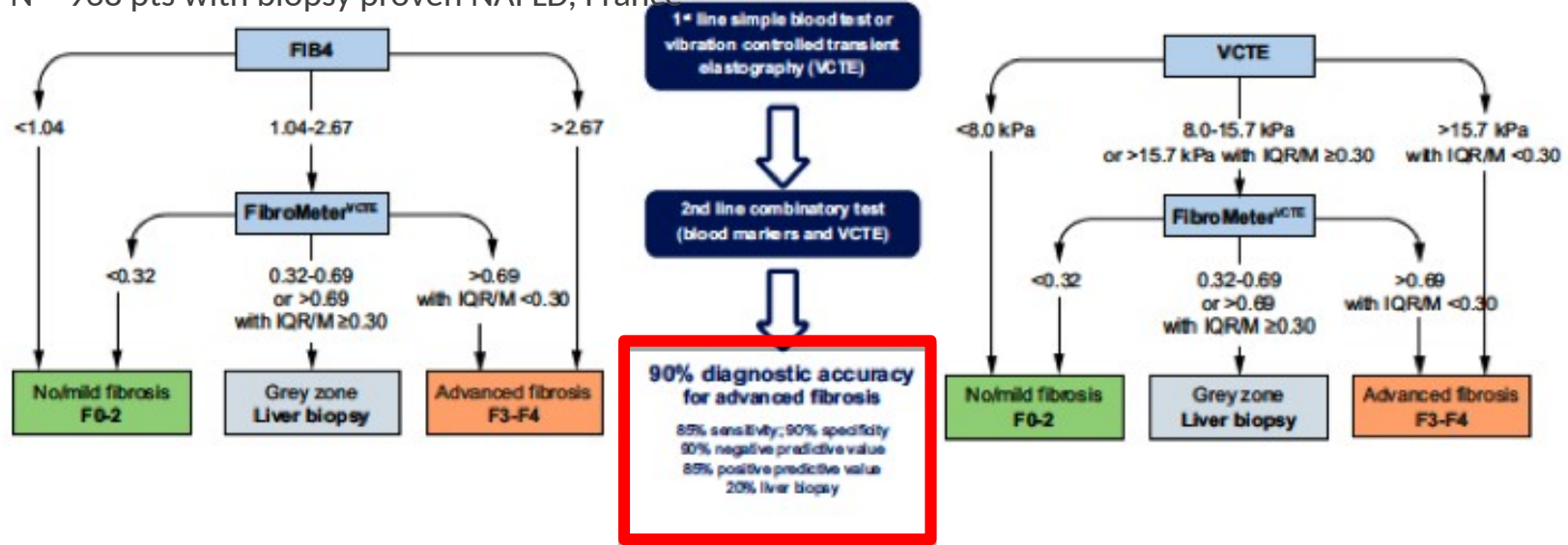
Unnecessary referral - reduced by 81%



# Second-line diagnostic tests in primary care settings

## ➤ Refine the indication for liver biopsy

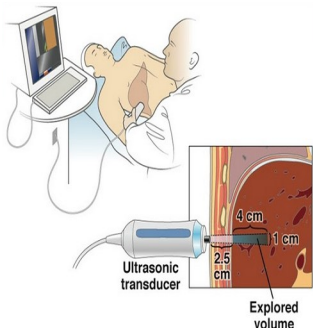
N = 938 pts with biopsy proven NAFLD, France



# Clinical case

## NON INVASIVE EVALUATION OF LIVER FIBROSIS

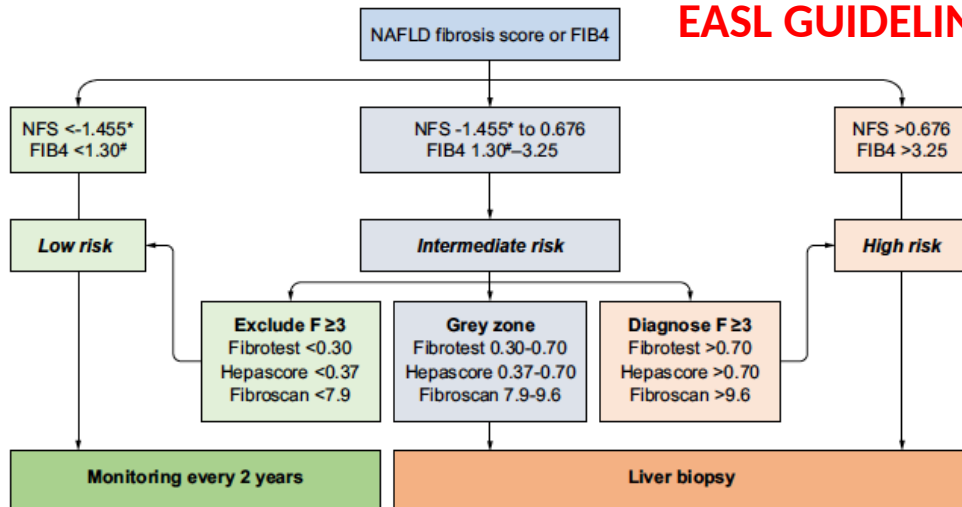
- FIB4 = 1.83
- NAFLD Fibrosis Score: 1.855



**FT = 0.63**  
**FS XL= 9.5 kPa;**  
**IQR = 13%;**  
**TDR = 90% (10/11)**

**ADVANCED FIBROSIS**

## EASL GUIDELINE



### Liver biopsy:

25 mm, 1 fragment, 11 PS  
 Macrovesicular steatosis 90%  
 Moderate lobular inflammation (grade 2)  
 Significant grade 2 ballooning  
 Portal and perisinusoidal fibrosis with septa  
 NAS = 7, **S3A4F3**

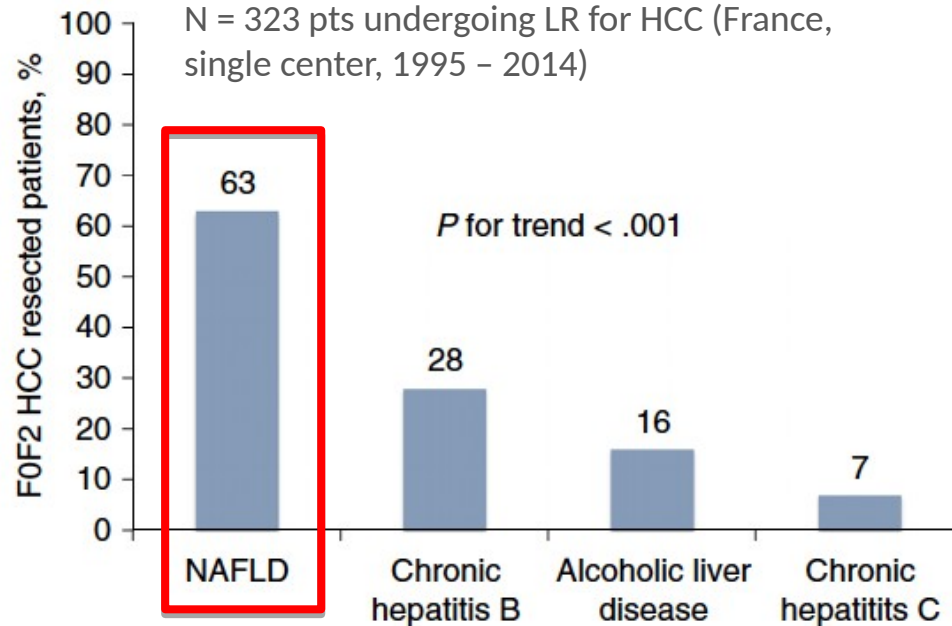
# CLINICAL CASE – MANAGEMENT



- Screen for HCC?
- High risk for extra hepatic cancer?
- Optimal management of comorbidities – weight, T2DM, OSA etc
- Consider inclusion in a NASH clinical trial
- Patient's education program

# Would you perform HCC screening?

## ➤ HCC often occur in the absence of cirrhosis



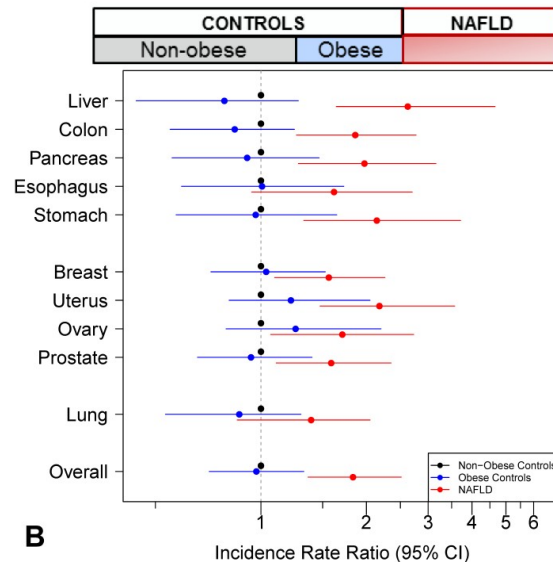
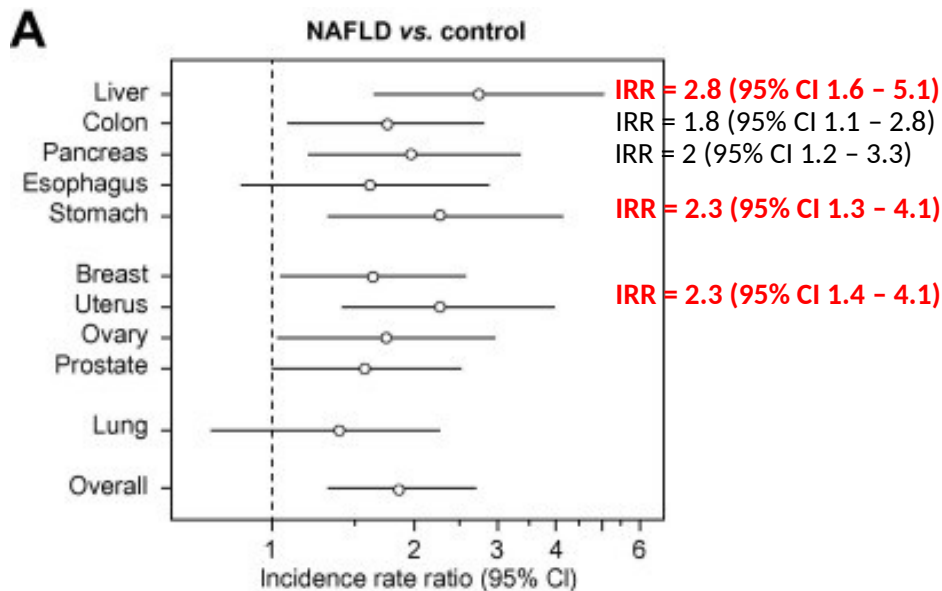
**Table 3. Recommendations for HCC surveillance: categories of adult patients in whom surveillance is recommended.**

1. Cirrhotic patients, Child-Pugh stage A and B\*
2. Cirrhotic patients, Child-Pugh stage C awaiting liver transplantation\*\*
3. Non-cirrhotic HBV carriers with active hepatitis or family history of HCC\*\*\*
4. Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis F3\*\*\*\*

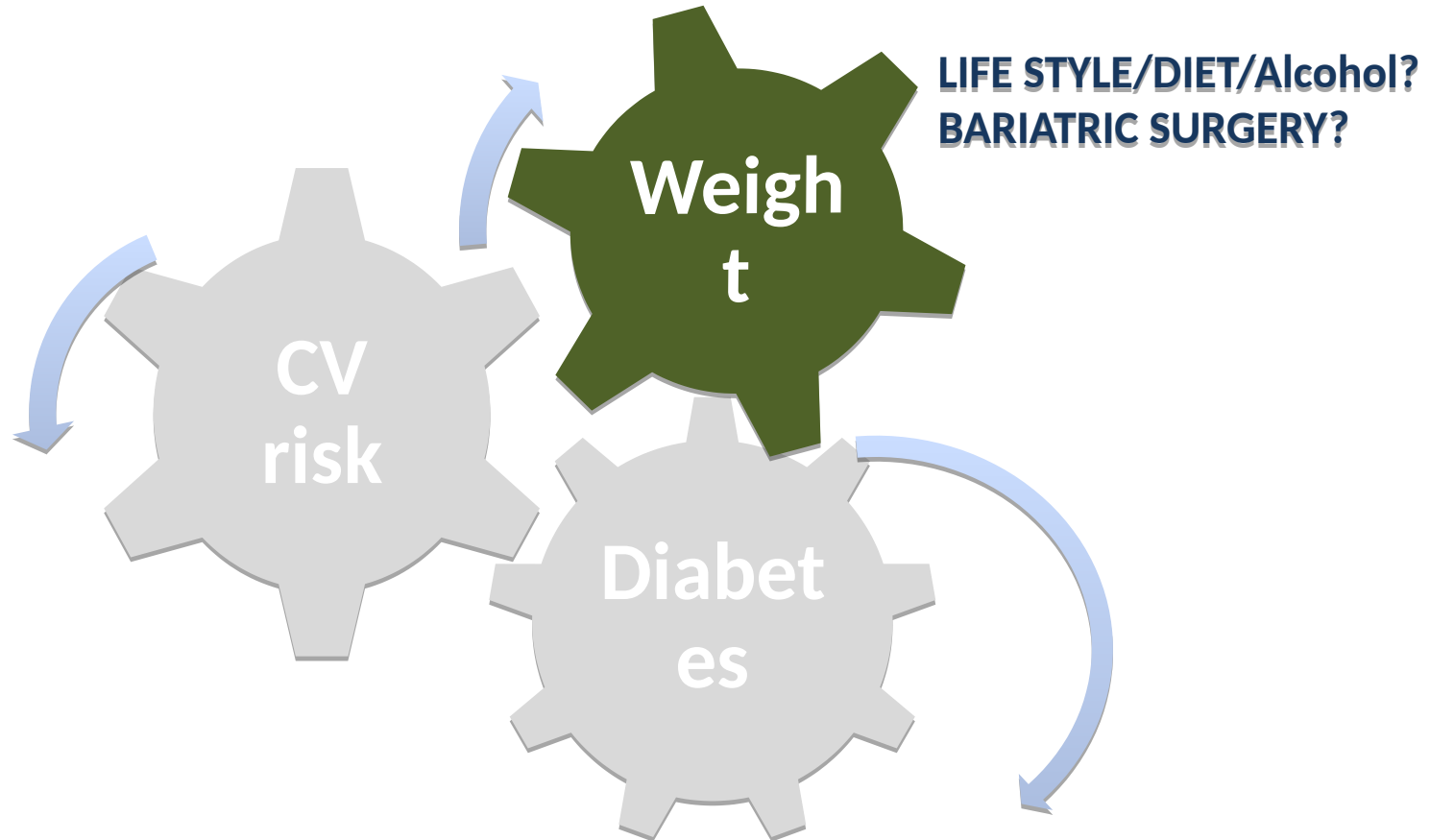
# Increased risk of incident extra hepatic cancer

N = 4722 individuals with NAFLD, Olmsted County  
Follow-up - 21 years

- NAFLD was associated with a higher risk of incident cancers (**IRR = 2.0**, 95% CI 1.5–2.9) vs. non obese controls;
- Obesity in the absence of NAFLD had minimal impact on malignancy risk (IRR = 1.0, 95% CI 0.8–1.4).



# COMORBIDITY MANAGEMENT/CONTROL



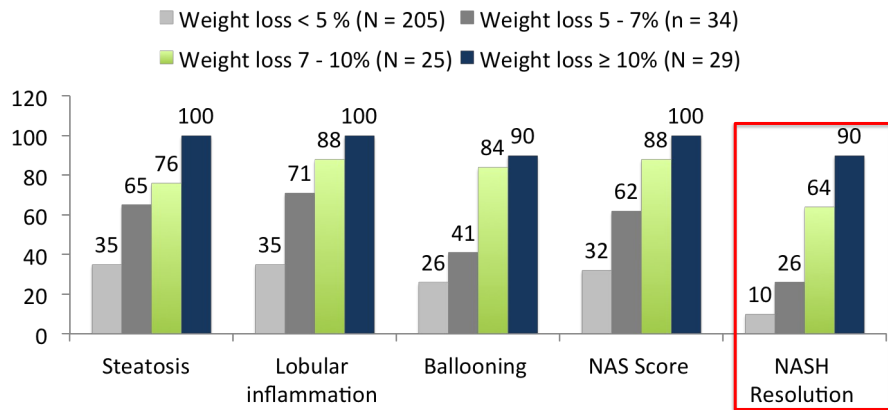
## Life style modifications

### 1. Histological improvement

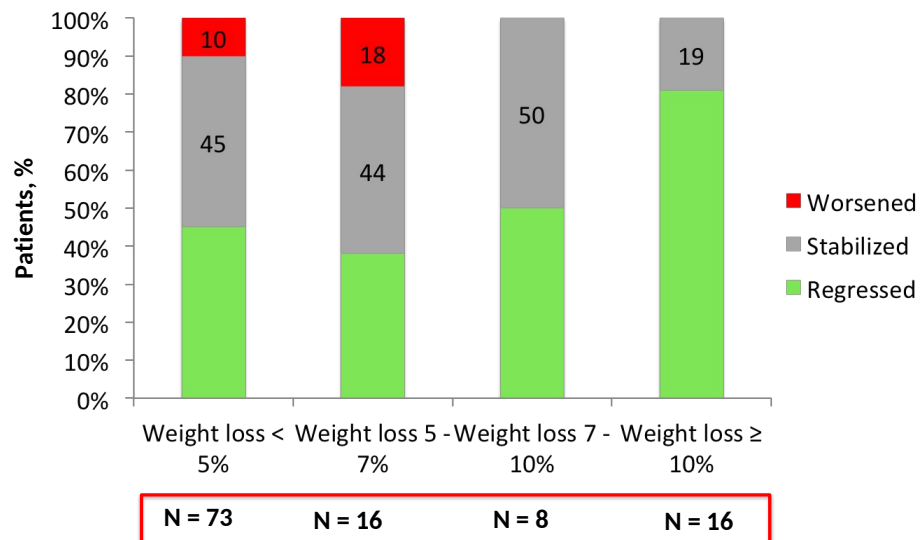
293 patients; 89% with paired liver biopsy

F/u: 52 weeks

Low-fat hypocaloric diet (- 750 kcal)



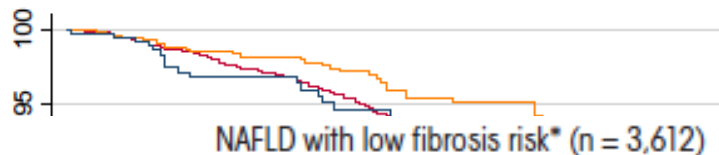
### 2. Fibrosis





# MODERATE ALCOHOL USE – GOOD OR BAD?

## PROTECTIVE EFFECT OF MODEST ALCOHOL CONSUMPTION ON OVERALL MORTALITY



|                                 | NAFLD with low fibrosis risk* (n = 3,612) |         | NAFLD with high fibrosis risk* (n = 328) |         |
|---------------------------------|-------------------------------------------|---------|------------------------------------------|---------|
|                                 | HR (95% CI)                               | P Value | HR (95% CI)                              | P Value |
| 0.5-1.4 drinks/day <sup>†</sup> | 0.46 (0.26–0.81)                          | 0.007   | 0.64 (0.29–1.35)                         | 0.241   |
| ≥1.5 drinks/day <sup>†</sup>    | 1.42 (0.92–2.18)                          | 0.112   | 1.08 (0.51–2.28)                         | 0.839   |
| Age                             | 1.09 (1.08–1.10)                          | <0.001  | 1.11 (1.07–1.14)                         | <0.001  |
| Male sex                        | 1.72 (1.23–2.42)                          | 0.002   | 1.23 (0.75–2.03)                         | 0.419   |
| Current smoking                 | 2.35 (1.61–3.45)                          | <0.001  | 1.68 (0.70–4.05)                         | 0.244   |

\*Low fibrosis risk defined as FIB-4 <1.79 and high fibrosis risk defined as FIB-4 >1.79.

<sup>†</sup>Compared with nondrinkers (average of <0.5 drink/day).

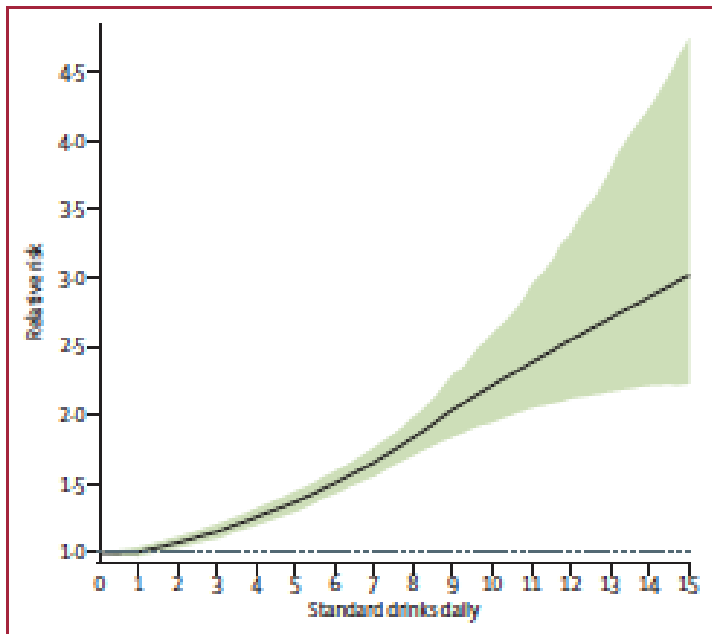
≥1.5 drinks/day 376      236      121      5  
 — <0.5 drink/day    — 0.5-1.4 drinks/day    — ≥1.5 drinks/day

2551 pts with NAFLD from NHANES DataBase 1988 – 2010

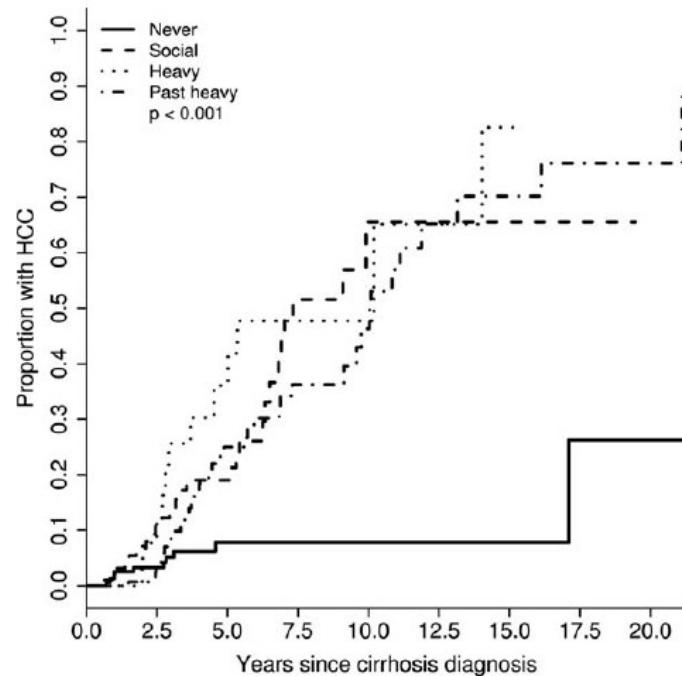
Hajifathalian, Hepatology 2019

# MODERATE ALCOHOL USE – GOOD OR BAD?

Weighted relative risk of alcohol for all attributable causes, by standard drinks consumed per day



Amount of alcohol consumption and risk of HCC

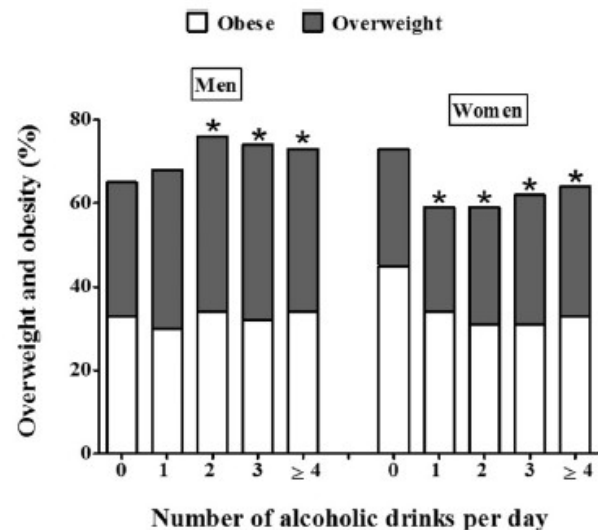


# MODERATE ALCOHOL USE – GOOD OR BAD?

Alcohol as a source of calories ... And the prevalence of overweight and obesity according to the number of drinks/day

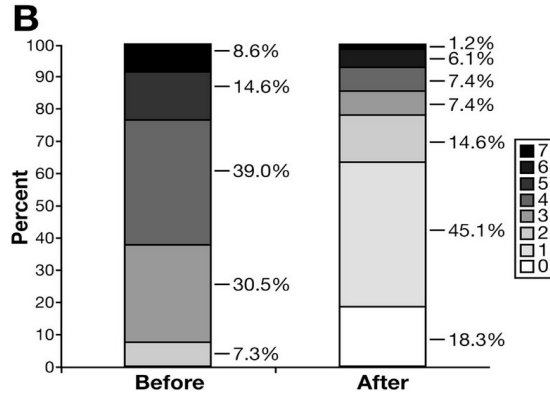
| Calories | # drinks<br>(1 unit=14 gm alcohol) | food                     |
|----------|------------------------------------|--------------------------|
| 140      | 2                                  | 1 scoop ice cream        |
| 280      | 4                                  | 1 cheeseburger           |
| 420      | 6                                  | 1 large slice cheesecake |
| 560      | 8                                  | 1 double cheese burger   |

- Alcohol (up to 4 drinks) increases appetite
- Alcohol increased high fat and high salt food intake
- Alcohol is oxidized preferentially
- This limits fat mobilization
- Clinical data on alcohol and weight gain are mixed

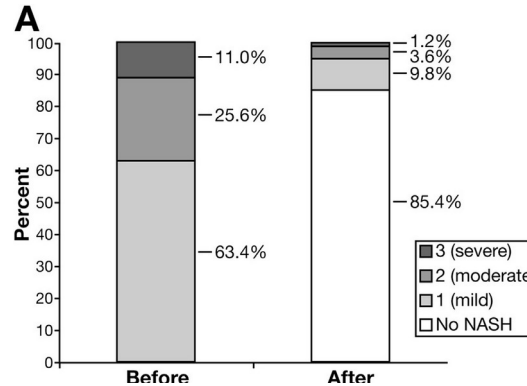


# BARIATRIC SURGERY

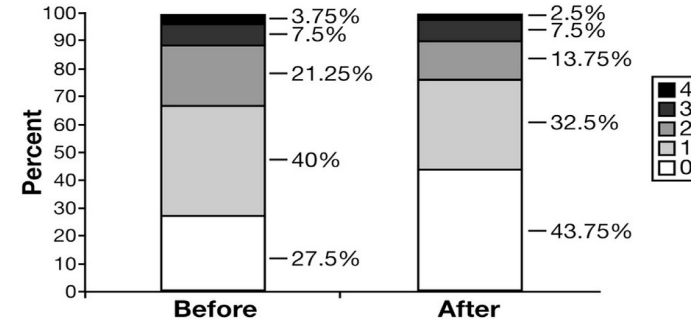
## Distribution of NAS



## NASH Resolution

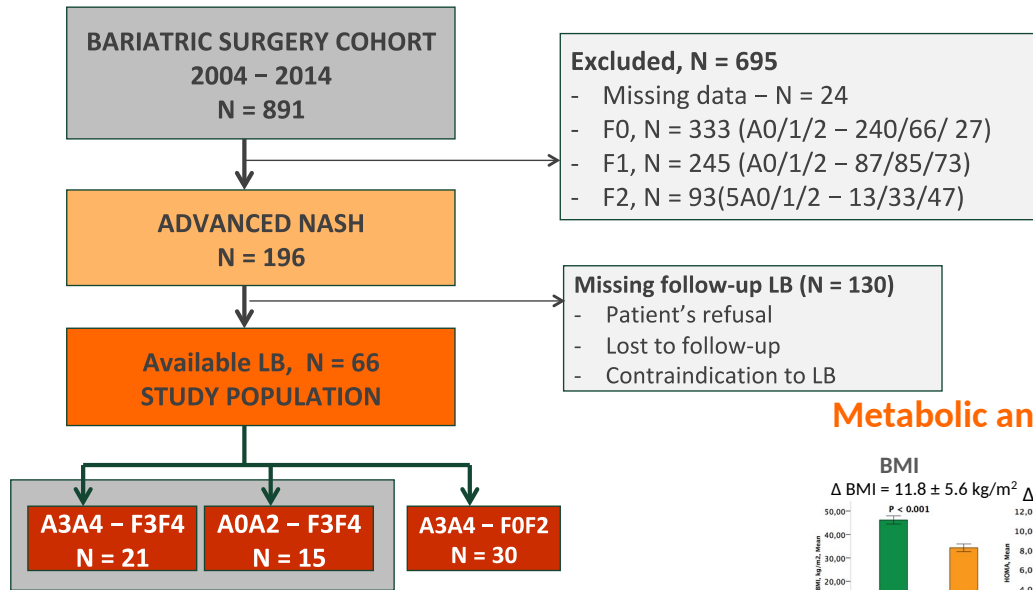


## Distribution of Fibrosis

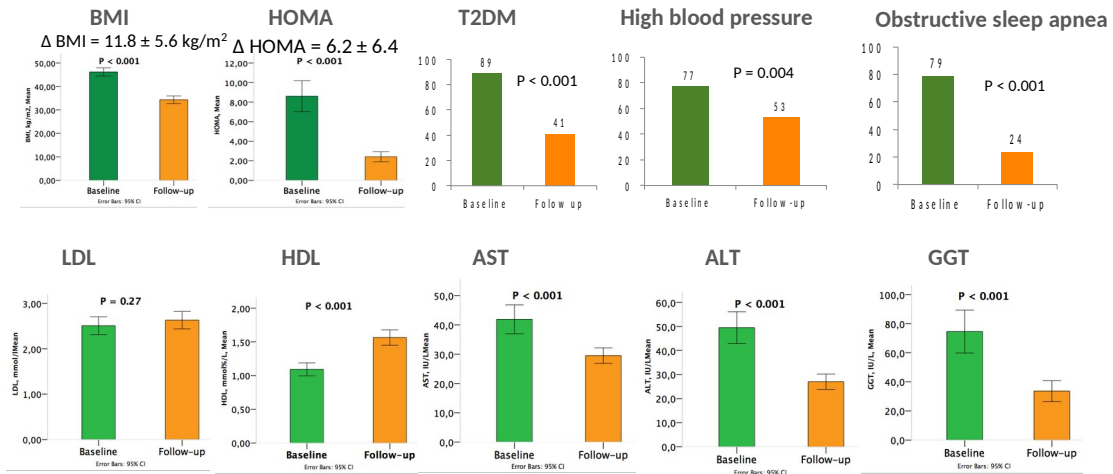


- ✓ NASH disappeared in 85.4% of cases
- ✓ Fibrosis improved in 46%.
- ✓ The rate of disappearance of NASH was higher in patients with mild NASH than in those with moderate or severe NASH
- ✓ 14.6% of patients had persistent NASH 1 year after bariatric surgery. These patients had significantly lower weight loss, higher NAS and refractory IR profile

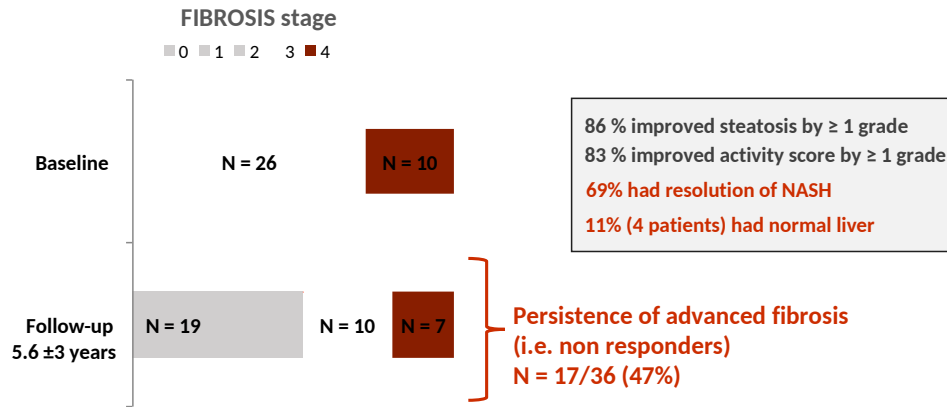
# BARIATRIC SURGERY... IN PATIENTS WITH ADVANCED FIBROSIS



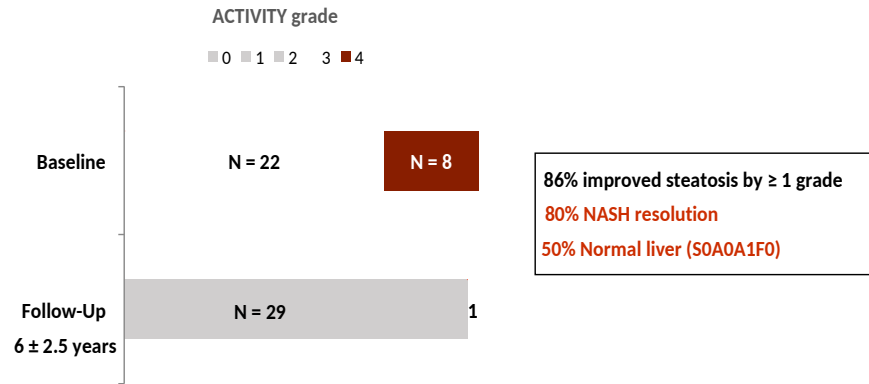
## Metabolic and LFT improvement (Pts with advanced NASH, N = 66)



## Histological evolution of patients with advanced fibrosis (F3/F4), N = 36



## Histological evolution of patients with high activity score at baseline without advanced fibrosis, A3A4/F0F2), N = 30



## Changes in liver and metabolic parameters according to fibrosis response

|                | Fibrosis responders | Fibrosis nonresponders | P    |
|----------------|---------------------|------------------------|------|
| $\Delta$ BMI   | $13 \pm 6$          | $10 \pm 6$             | 0.15 |
| $\Delta$ HOMA  | $6.6 \pm 6.5$       | $6.7 \pm 7.5$          | 0.96 |
| $\Delta$ HbA1c | $1.3 \pm 1.13$      | $0.8 \pm 1.3$          | 0.30 |
| $\Delta$ ALT   | $25 \pm 23$         | $30 \pm 36$            | 0.65 |
| $\Delta$ GGT   | $51 \pm 43$         | $59 \pm 63$            | 0.67 |
| $\Delta$ LDL   | $-0.2 \pm 0.9$      | $-0.15 \pm 0.9$        | 0.72 |
| $\Delta$ TG    | $0.7 \pm 0.6$       | $0.6 \pm 1.5$          | 0.88 |
| $\Delta$ HDL   | $-0.5 \pm 0.3$      | $-0.3 \pm 0.6$         | 0.26 |

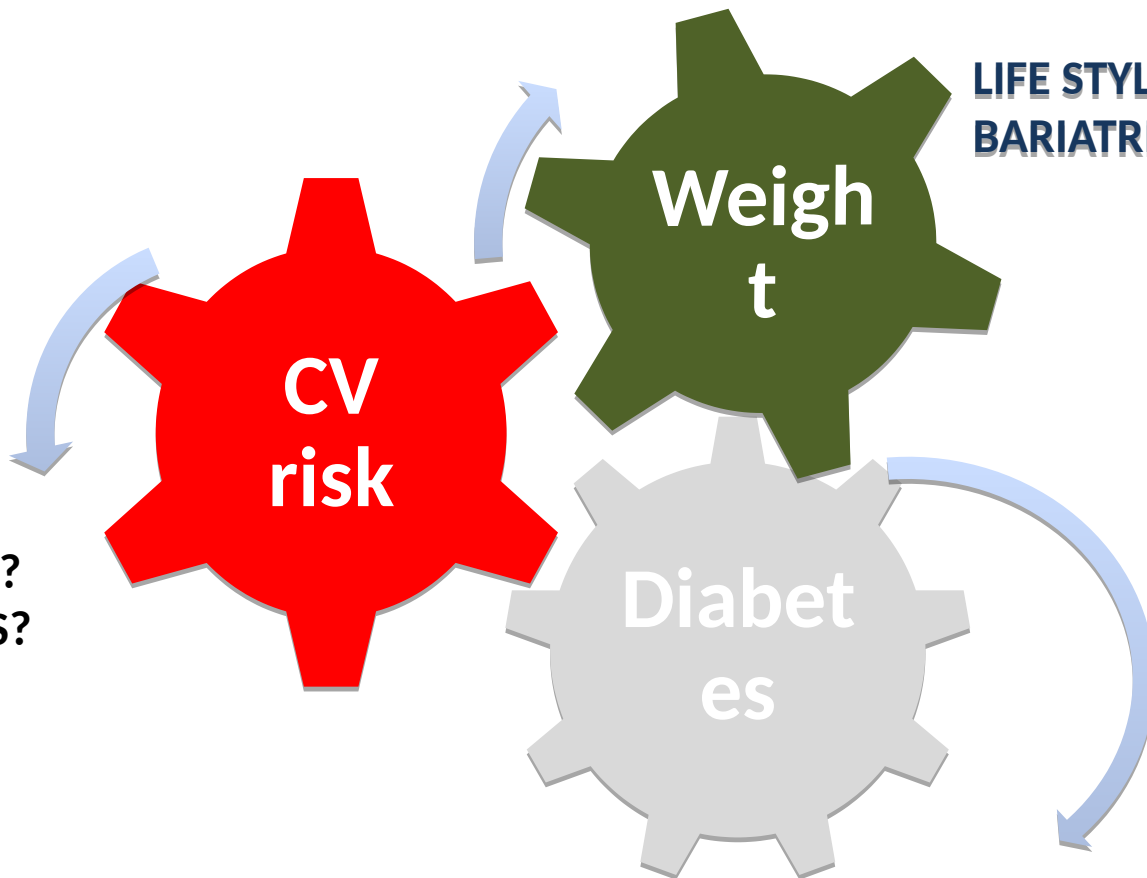
## Independent predictors of persistent fibrosis

|                   | OR, 95% CI          | P     |
|-------------------|---------------------|-------|
| Age               | 1.08 (1.001 - 1.17) | 0.046 |
| Sleeve            | 7.19 (2.17 - 23.8)  | 0.001 |
| Sex               | 0.80 (0.26 - 2.45)  | 0.70  |
| Baseline diabetes | 0.41 (0.096 - 1.77) | 0.236 |
| $\Delta$ BMI      | 1.017 (0.94 - 1.10) | 0.66  |

# COMORBIDITY MANAGEMENT/CONTROL

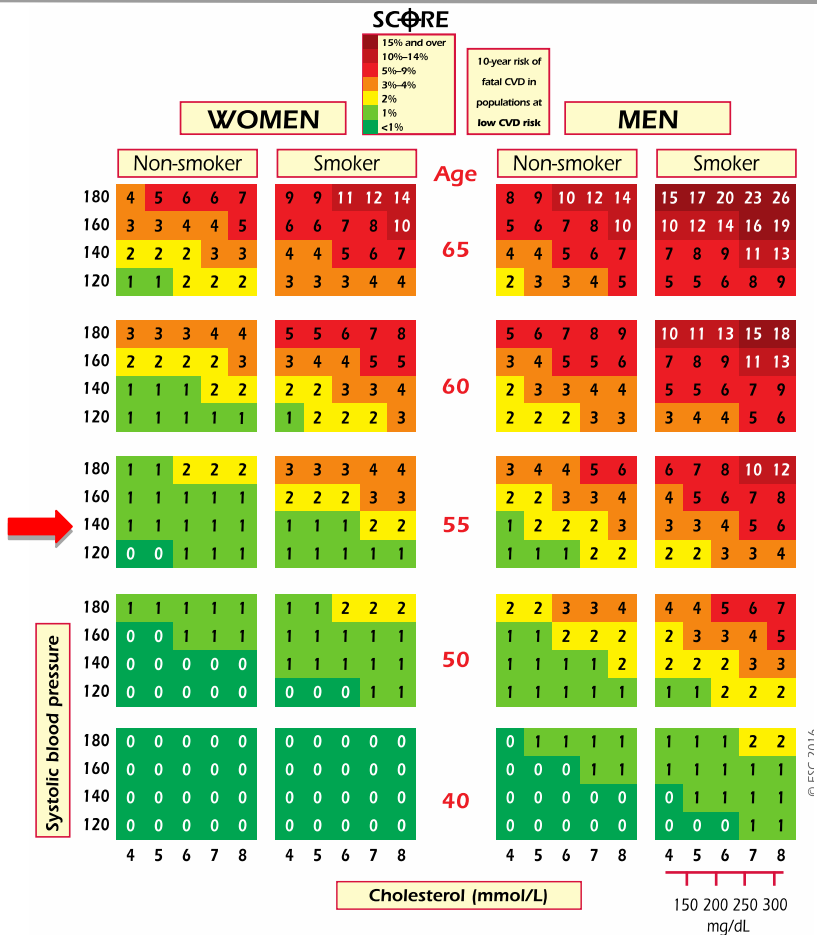


**EVALUATE CV RISK?  
CONSIDER STATINS?**



**LIFE STYLE/DIET/Alcohol?  
BARIATRIC SURGERY?**

# EVALUATION OF CV RISK



## Risk categories:

Low - < 1%

Moderate - 1 - 5 %

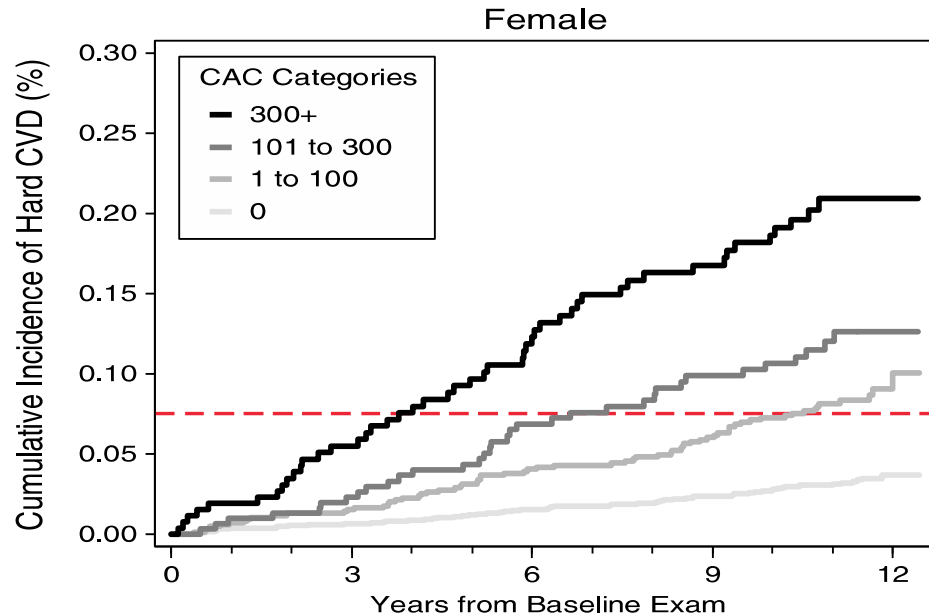
High - 5 - 10%

Very high - > 10%

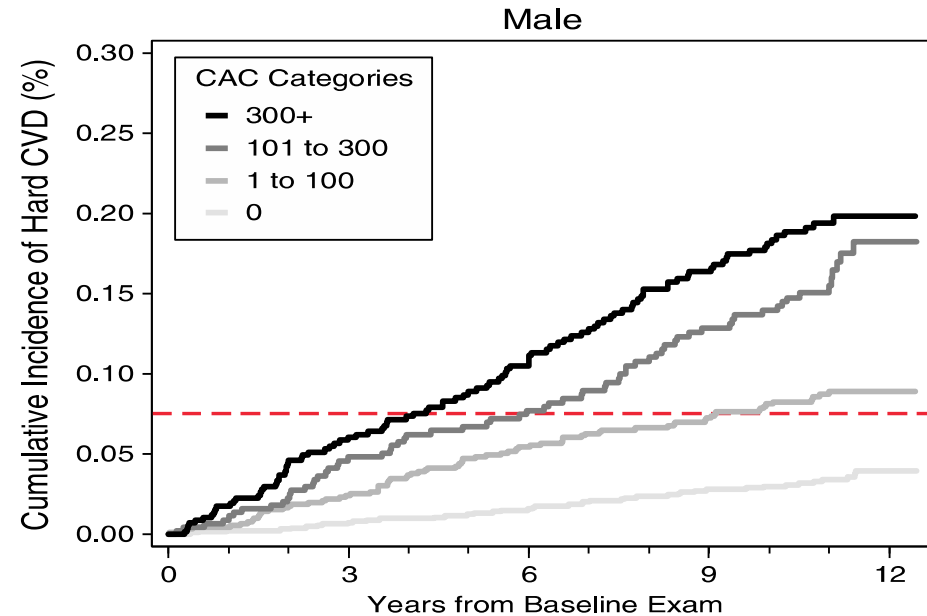
**Patients with :** documented CVD, type 2 diabetes, high level of individual risk factors or CKD, **are already considered at very high risk for CVD and do not need the use of risk score**



# Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events



N=6,783. Red dashed line shows 7.5% risk.



# EVALUATION OF CV RISK

**CORONARY CALCIUM SCORE = 581 AGATSTON UNITS**

<https://www.mesa-nhlbi.org/MESACHDRisk/MesaRiskScore/RiskScore.aspx>

**MESA 10-Year CHD Risk with Coronary Artery Calcification** [Back to CAC Tools](#)

|                                                                                  |                                      |                                         |
|----------------------------------------------------------------------------------|--------------------------------------|-----------------------------------------|
| 1. Gender                                                                        | Male <input type="radio"/>           | Female <input checked="" type="radio"/> |
| 2. Age (45-85 years)                                                             | 57                                   | Years                                   |
| 3. Coronary Artery Calcification                                                 | 581                                  | Agatston                                |
| 4. Race/Ethnicity                                                                | <b>Choose One</b>                    |                                         |
|                                                                                  | Caucasian                            | <input checked="" type="radio"/>        |
|                                                                                  | Chinese                              | <input type="radio"/>                   |
|                                                                                  | African American                     | <input type="radio"/>                   |
|                                                                                  | Hispanic                             | <input type="radio"/>                   |
| 5. Diabetes                                                                      | Yes <input checked="" type="radio"/> | No <input type="radio"/>                |
| 6. Currently Smoke                                                               | Yes <input type="radio"/>            | No <input checked="" type="radio"/>     |
| 7. Family History of Heart Attack<br>(History in parents, siblings, or children) | Yes <input type="radio"/>            | No <input checked="" type="radio"/>     |
| 8. Total Cholesterol                                                             | 225.4                                | mg/dL or 5.83 mmol/L                    |
| 9. HDL Cholesterol                                                               | 37                                   | mg/dL or 1.0 mmol/L                     |
| 10. Systolic Blood Pressure                                                      | 150                                  | mmHg or 20.0 kPa                        |
| 11. Lipid Lowering Medication                                                    | Yes <input type="radio"/>            | No <input checked="" type="radio"/>     |
| 12. Hypertension Medication                                                      | Yes <input checked="" type="radio"/> | No <input type="radio"/>                |

Calculate 10-year CHD risk

- The estimated 10-year risk of a CHD including coronary calcium is **19.7%**.
- The estimated 10-year risk of a CHD event if we did not factor in their coronary calcium score would be **7.9%**.

## Control for CV risk factors (follow National/international Guidelines):

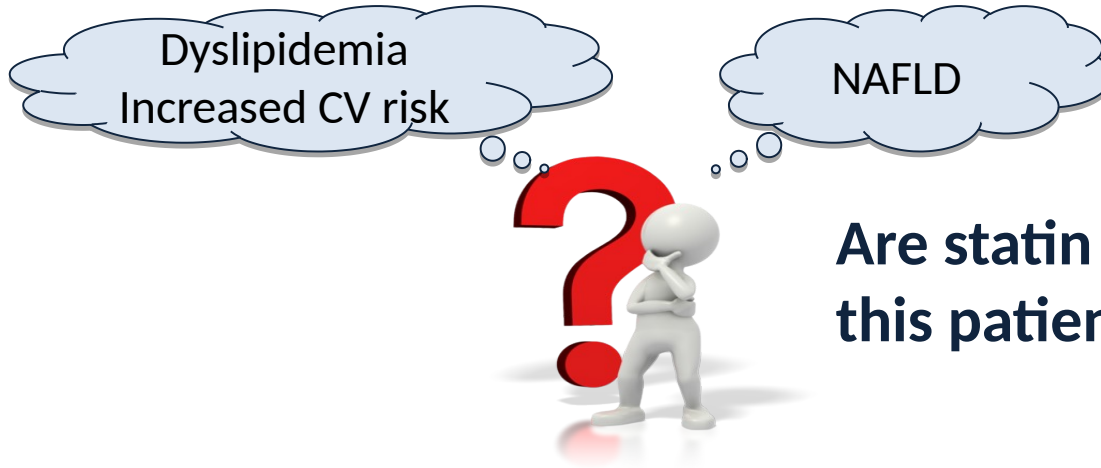
- ✧ Physical activity/Weight control
- ✧ Smoking cessation
- ✧ Control for HBP
- ✧ Lipids control

### Classification of physical activity

| Absolute intensity |         |                                                                                                                                                                                                       | Relative intensity |
|--------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| Intensity          | MET     | Examples                                                                                                                                                                                              | %HRmax             |
| Light              | 1.1–2.9 | Walking <4.7 km/h, light household work.                                                                                                                                                              | 50–63              |
| Moderate           | 3–5.9   | Walking briskly (4.8–6.5 km/h), slow cycling (15 km/h), painting/decorating, vacuuming, gardening (mowing lawn), golf (pulling clubs in trolley), tennis (doubles), ballroom dancing, water aerobics. | 64–76              |
| Vigorous           | ≥6      | Race-walking, jogging or running, bicycling >15 km/h, heavy gardening (continuous digging or hoeing), swimming laps, tennis (single).                                                                 | 77–93              |

### ESC Guideline for primary CV prevention

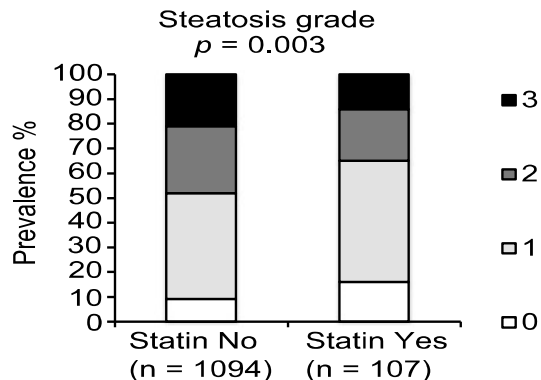
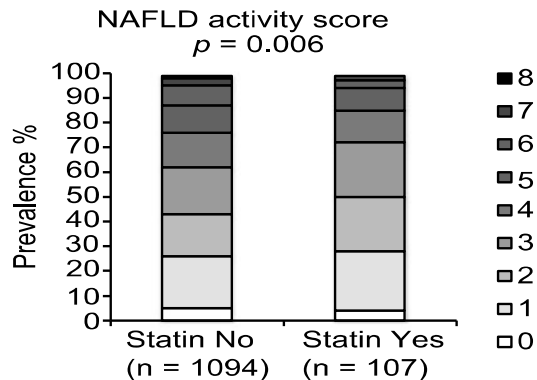
|                                                                     |                                                                                                                                                                                                        |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Smoking</b>                                                      | No exposure to tobacco in any form.                                                                                                                                                                    |
| <b>Diet</b>                                                         | Low in saturated fat with a focus on wholegrain products, vegetables, fruit and fish.                                                                                                                  |
| <b>Physical activity</b>                                            | At least 150 minutes a week of moderate aerobic PA (30 minutes for 5 days/week) or 75 minutes a week of vigorous aerobic PA (15 minutes for 5 days/week) or a combination thereof.                     |
| <b>Body weight</b>                                                  | BMI 20–25 kg/m <sup>2</sup> . Waist circumference <94 cm (men) or <80 cm (women).                                                                                                                      |
| <b>Blood pressure</b>                                               | <140/90 mmHg <sup>a</sup>                                                                                                                                                                              |
| <b>Lipids<sup>b</sup></b><br>LDL <sup>c</sup> is the primary target | <b>Very high-risk:</b> <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL) <sup>d</sup>                                           |
|                                                                     | <b>High-risk:</b> <2.6 mmol/L (<100 mg/dL), or a reduction of at least 50% if the baseline is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL)<br><b>Low to moderate risk:</b> <3.0 mmol/L (<115 mg/dL). |
| HDL-C                                                               | No target but >1.0 mmol/L (>40 mg/dL) in men and >1.2 mmol/L (>45 mg/dL) in women indicate lower risk.                                                                                                 |
| Triglycerides                                                       | No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors.                                                                          |
| <b>Diabetes</b>                                                     | HbA1c <7%. (<53 mmol/mol)                                                                                                                                                                              |



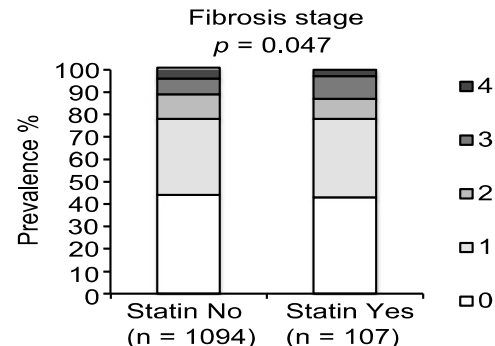
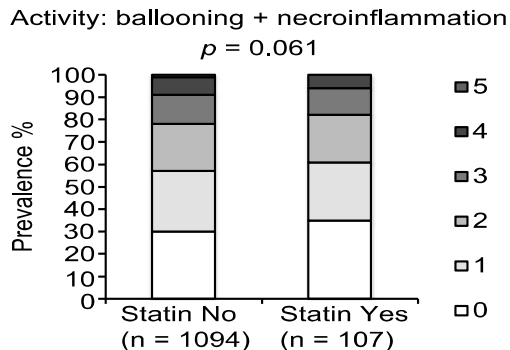
**Are statin recommended in this patient?**

- No, because of safety issues
- Yes for reducing CV risk
- YES to ameliorate liver histology?

# Statins use – protection from severe form of NAFLD



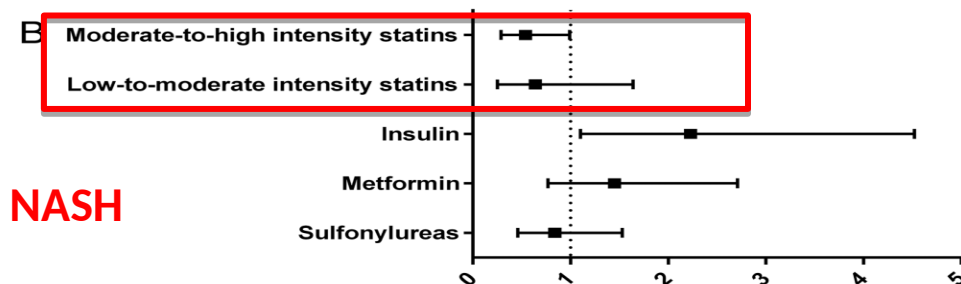
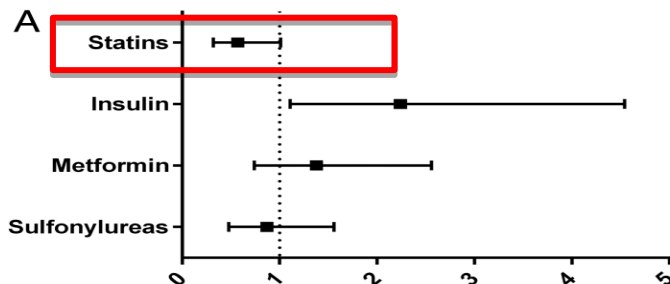
- ✓ Multicenter European cohort
  - ✓ 1201 subjects
  - ✓ 107 (9%) taking statins for  $\geq 6$  months; moderate intensity
- 73%



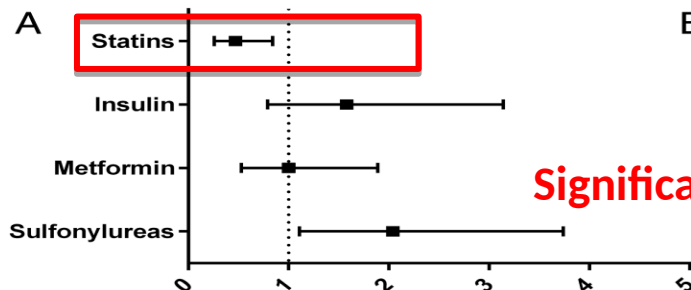
# Statins use – protection from severe form of NAFLD

346 pts with T2DM and histological proven NAFLD

57% had NASH, 48% had significant fibrosis; 45% were taking statins



**NASH**



**Significant fibrosis**

## CHOICE OF STATINS ...

### Definition of High, Moderate and Low Intensity Statin Agents and Doses

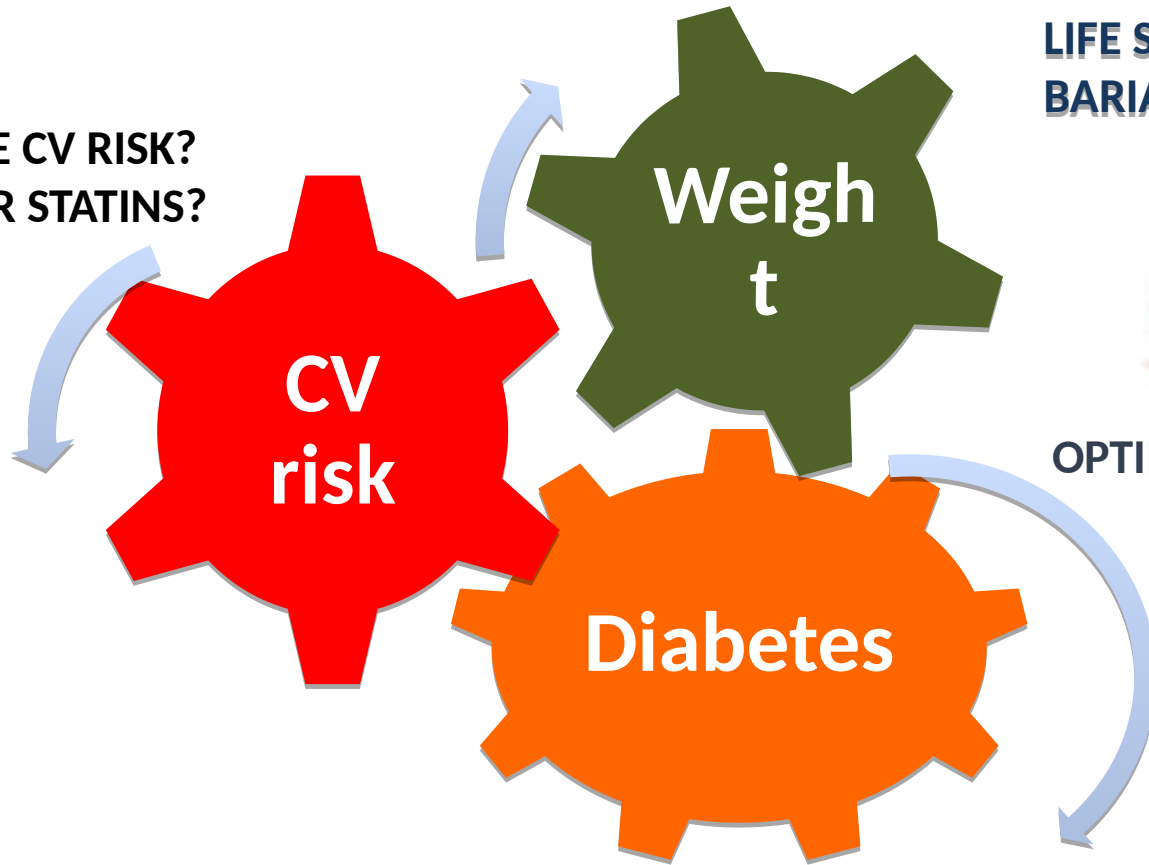
| High-Intensity                                                                                                                                                                                                                       | Moderate-Intensity                                                                                                                                                                                                                                      | Low-Intensity                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| Daily dose lowers LDL-C on average, by $\sim \geq 50\%$                                                                                                                                                                              | Daily dose lowers LDL-C on average, by $\sim 30$ to $<50\%$                                                                                                                                                                                             | Daily dose lowers LDL-C on average, by $<30\%$                                                                                                |
| <b>Atorvastatin (40)–80 mg</b><br><b>Rosuvastatin 20 (40) mg</b>                                                                                                                                                                     | <b>Atorvastatin 10 (20) mg</b><br><b>Rosuvastatin (5) 10 mg</b><br><b>Simvastatin 20–40 mg</b><br><b>Pravastatin 40 (80) mg</b><br><b>Lovastatin 40 mg</b><br><i>Fluvastatin XL 80 mg</i><br><b>Fluvastatin 40 mg bid</b><br><i>Pitavastatin 2–4 mg</i> | <i>Simvastatin 10 mg</i><br><b>Pravastatin 10–20 mg</b><br><b>Lovastatin 20 mg</b><br><i>Fluvastatin 20–40 mg</i><br><i>Pitavastatin 1 mg</i> |
| Specific statins and doses are noted in <b>bold</b> that were evaluated in randomized controlled trials. Statins and doses that are approved by the U.S. FDA but were not tested in the RCTs reviewed are listed in <i>italics</i> . |                                                                                                                                                                                                                                                         |                                                                                                                                               |

Stone NJ, et al, J Amer Coll Card 2013, doi10.1016/j.jacc.2013.11.002

ATORVASTATIN 10 MG

# COMORBIDITY MANAGEMENT/CONTROL

EVALUATE CV RISK?  
CONSIDER STATINS?



LIFE STYLE/DIET/Alcohol?  
BARIATRIC SURGERY?

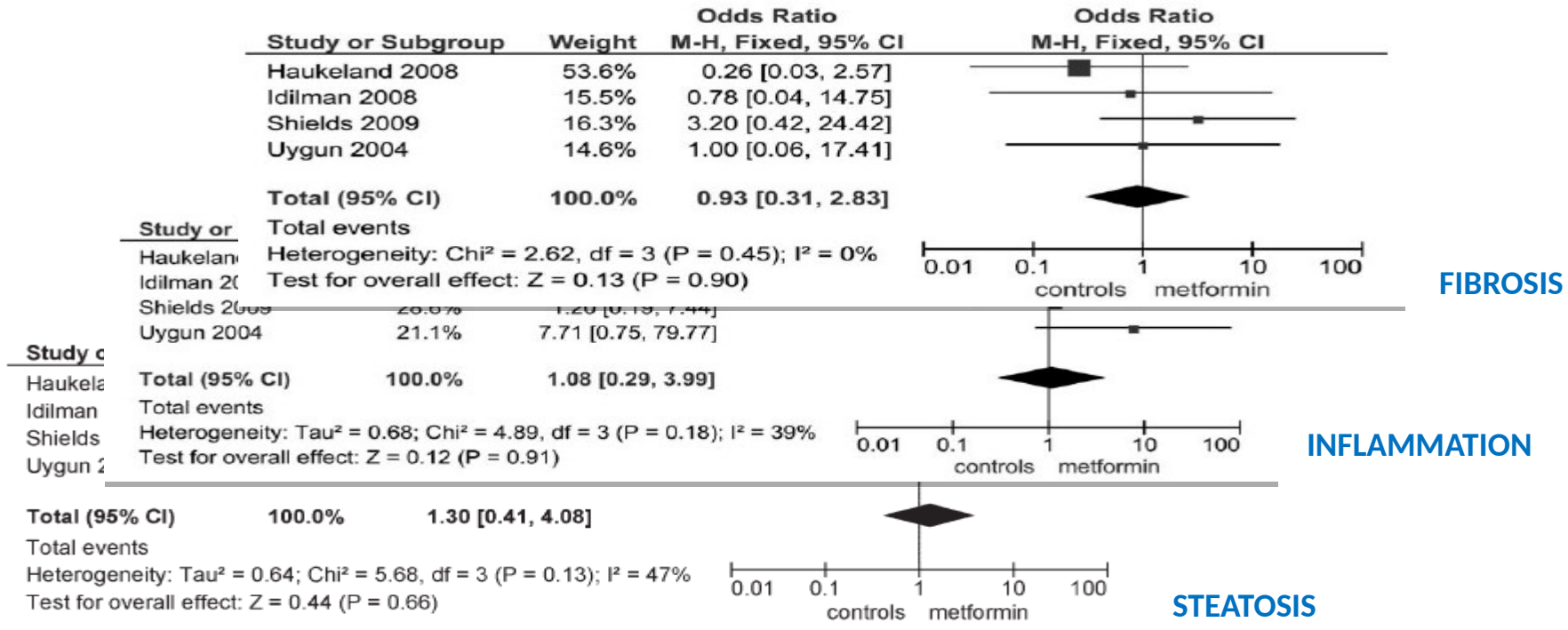


OPTIMIZE T2DM CONTROL:

Metformine?  
GLP1?



# A requiem for Metformin....



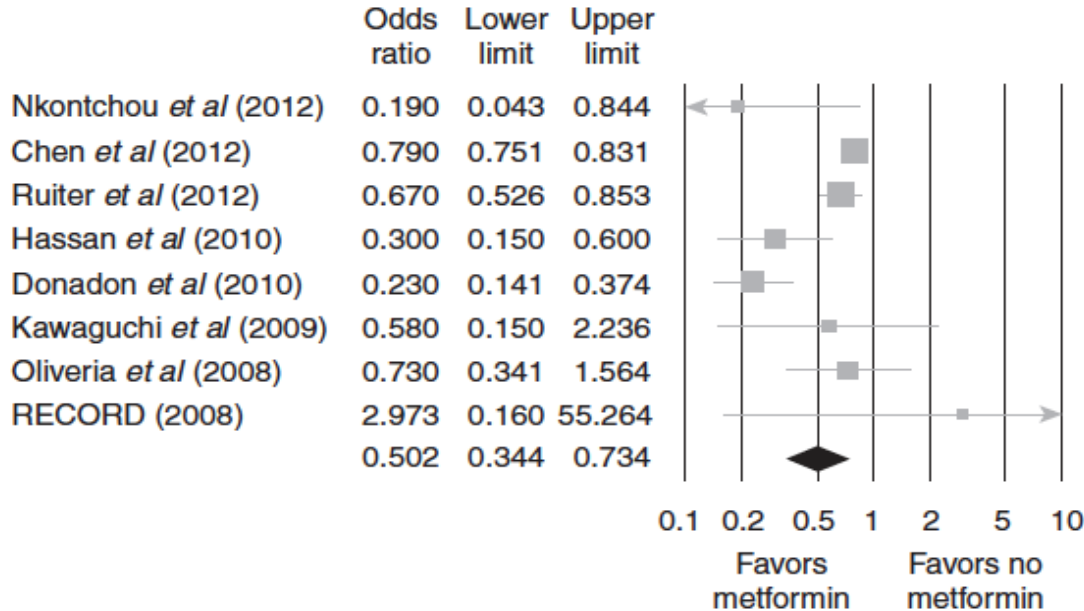
# ANTIDIABETIC MEDICATION AND THE RISK OF HCC

MA of 10 studies reporting 22 650 cases of HCC among 334 307 patients with T2DM

## Metformin and risk of hepatocellular cancer

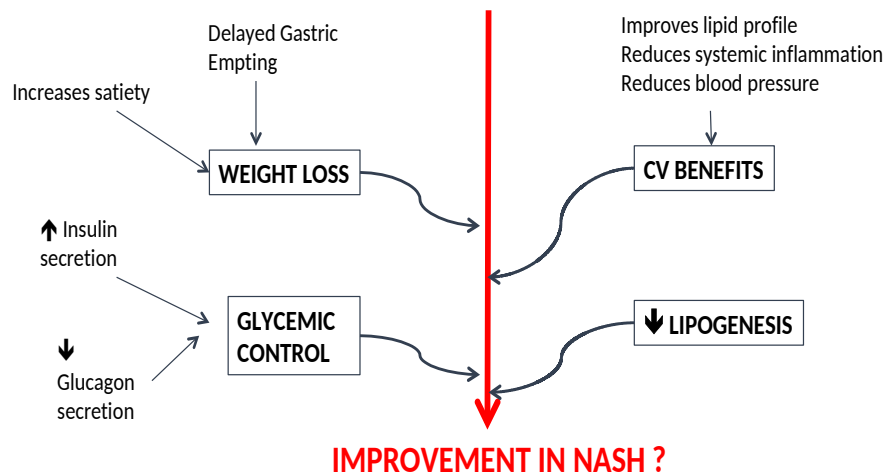
### Study name

### Odds ratio and 95% CI



**Metformin: ↓50%**  
**Sulfonylureas: ↑61%**  
**Insuline: ↑161%**  
**TZD - no changes**

# GLP1 ANTAGONISTS AND NAFLD ...



Armstrong, The  
Lancet 2015

|                                                              | Liraglutide | Placebo    | Relative risks or mean changes (95% CI) from baseline to 48 weeks (liraglutide vs placebo) | p value* |
|--------------------------------------------------------------|-------------|------------|--------------------------------------------------------------------------------------------|----------|
| <b>Primary outcome</b>                                       |             |            |                                                                                            |          |
| Number of patients with paired liver biopsies                | 23          | 22         | ..                                                                                         | ..       |
| Patients with resolution of non-alcoholic steatohepatitis    | 9 (39%)     | 2 (9%)     | 4.3 (1.0 to 17.7)                                                                          | 0.019    |
| <b>Changes from baseline in histopathological parameters</b> |             |            |                                                                                            |          |
| Total NAFLD activity score                                   |             |            |                                                                                            |          |
| Change in score                                              | -1.3 (1.6)  | -0.8 (1.2) | -0.5 (-1.3 to 0.3)                                                                         | 0.24     |
| Patients with improvement                                    | 17 (74%)    | 14 (64%)   | 1.2 (0.8 to 1.7)                                                                           | 0.46     |
| Hepatocyte ballooning score                                  |             |            |                                                                                            |          |
| Mean change                                                  | -0.5 (0.7)  | -0.2 (0.6) | -0.3 (-0.7 to 0.1)                                                                         | 0.15     |
| Patients with improvement                                    | 14 (61%)    | 7 (32%)    | 1.9 (1.0 to 3.8)                                                                           | 0.05     |
| Steatosis                                                    |             |            |                                                                                            |          |
| Change in score                                              | -0.7 (0.8)  | -0.4 (0.8) | -0.2 (-0.6 to 0.2)                                                                         | 0.32     |
| Patients with improvement                                    | 19 (83%)    | 10 (45%)   | 1.8 (1.1 to 3.0)                                                                           | 0.009    |
| Lobular inflammation                                         |             |            |                                                                                            |          |
| Change in score                                              | -0.2 (0.6)  | -0.2 (0.5) | -0.01 (-0.3 to 0.3)                                                                        | 0.97     |
| Patients with improvement                                    | 11 (48%)    | 12 (55%)   | 0.9 (0.5 to 1.6)                                                                           | 0.65     |
| Kleiner fibrosis stage                                       |             |            |                                                                                            |          |
| Change in score                                              | -0.2 (0.8)  | 0.2 (1.0)  | -0.4 (-0.8 to 0.1)                                                                         | 0.11     |
| Patients with improvement                                    | 6 (26%)     | 3 (14%)    | 1.9 (0.5 to 6.7)                                                                           | 0.46†    |
| Patients with worsening                                      | 2 (9%)      | 8 (36%)    | 0.2 (0.1 to 1.0)                                                                           | 0.04†    |

## Liver biopsy:

25 mmHg, 1 fragment, 11 PS  
Macrovesicular steatosis 90%  
Moderate lobular inflammation  
Significant grade 2 ballooning  
Portal and perisinusoidal fibrosis with septa  
NAS = 7, **S3A4F3**

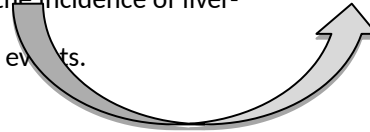


## **SIMTUZUMAB CLINICAL TRIAL**

### Primary objective:

F3: change in hepatic collagen  
content and progression to  
cirrhosis.

F4:  $\Delta$  HVPG ; the incidence of liver-  
related clinical events.

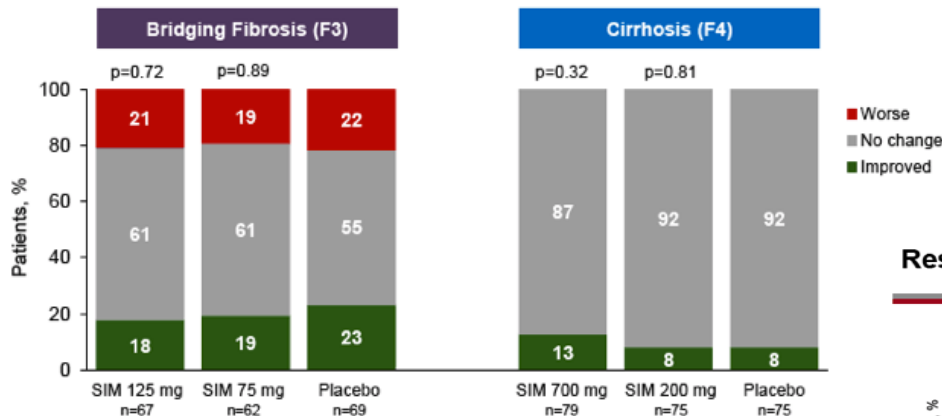


### **EOT LB 2016:**

HVPG = 18 mmHg ;  
16 mm length, 12 fragments  
Regeneration nodules, annular  
fibrosis  
50% steatosis; minimal lobular  
inflammation, no ballooning  
**S2A1F4**

# Simtuzumab Is Ineffective for Patients With Bridging Fibrosis or Compensated Cirrhosis Caused by Nonalcoholic Steatohepatitis

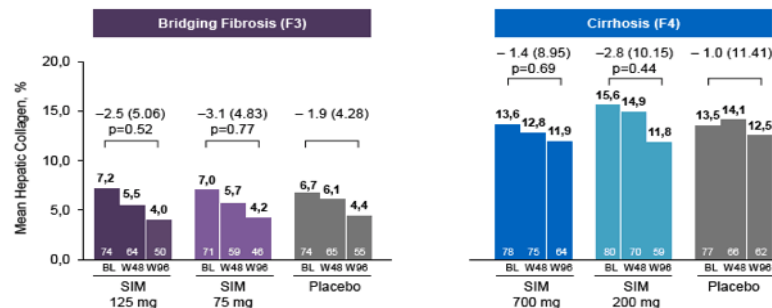
## Results: NASH CRN Fibrosis Stage (Week 96)



♦ SIM had no effect on fibrosis stage through Week 96

Last observation carried forward if Week 96 biopsy missing. p-values for comparisons between SIM and placebo adjusted for stratification fac

## Results: Hepatic Collagen Content

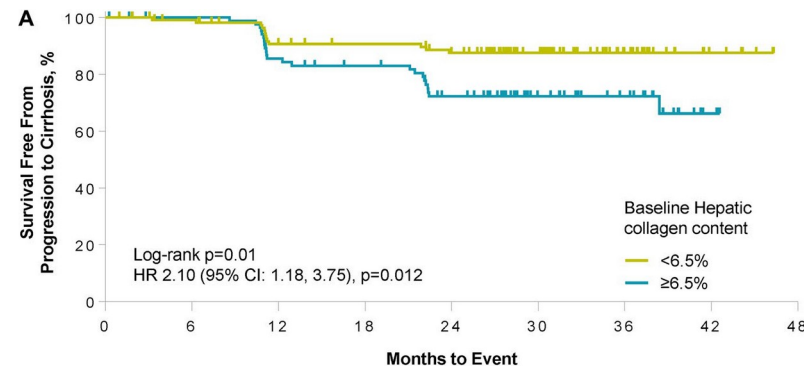
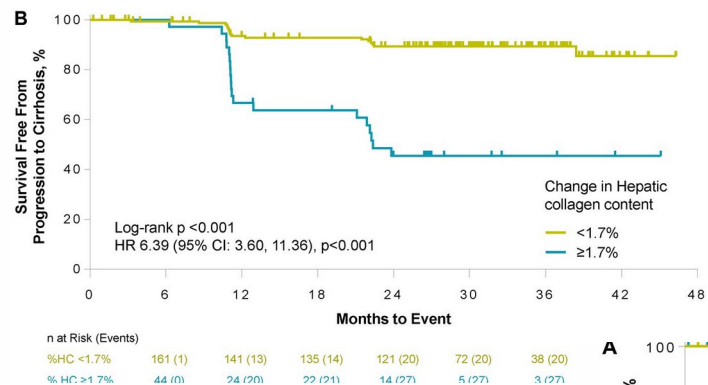


♦ SIM had no effect on hepatic collagen content

p-values for comparison of change from baseline (BL) at Week 96 (W96) between SIM vs placebo.

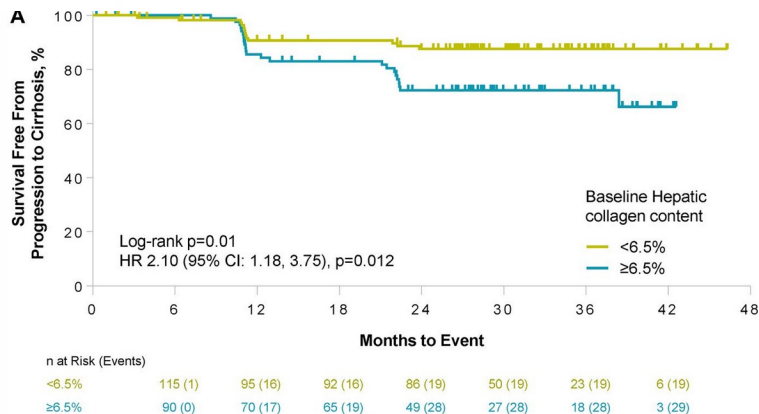
# The Natural History of Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: Data From the Simtuzumab Trials

- ✓ 20% of patients with bridging fibrosis progressed to cirrhosis during a median 29 months follow-up
- ✓ 21% of patients with bridging fibrosis had  $\geq 1$  stage fibrosis regression



## Factors associated with progression to cirrhosis were:

- baseline hepatic collagen content,
- changes in baseline hepatic collagen content,
- baseline ELF



**S3A4F3**

**Plt = 175 000**

Albumin = 36

Creatinin = 86 $\mu$ mol/l

HbA1c = 7.5 mmHg

BiliT = 29  $\mu$ mol/l

CT = 4.01 mmol/l ; TG =

1.70 mmol/l;

AST = 36 IU/l, ALT = 41

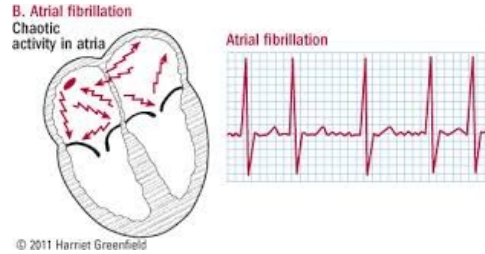
IU/l, GGT = 95 IU/l

**LSM = 27kPa**

**CHILD = A5**

**MELD = 11**

## SIMTUZUMAB CLINICAL TRIAL



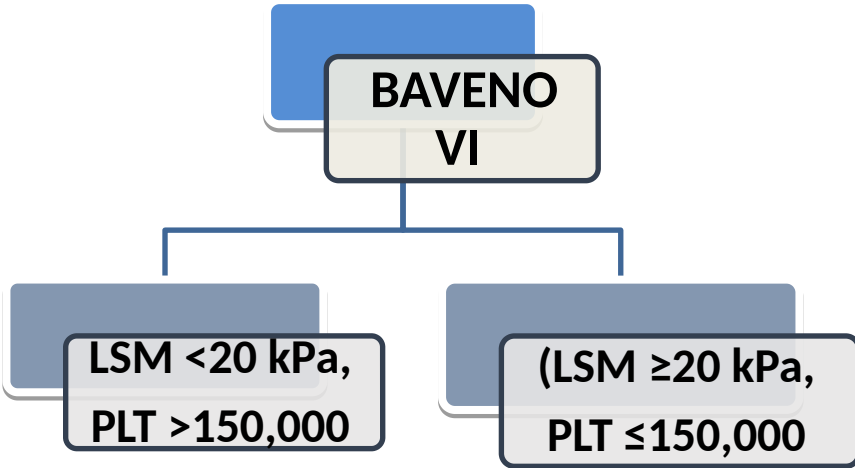
**EEC**  
**CARVEDILOL,**  
**ANTICOAGULANTS**

## COMPENSATED CIRRHOSIS S2A1F4

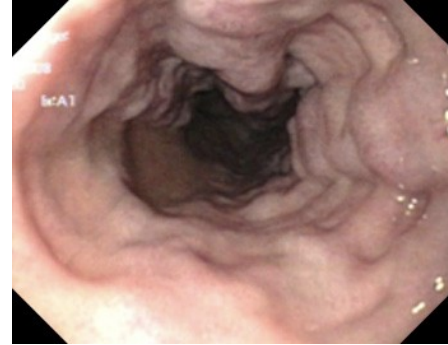


**WOULD YOU PERFORM SCREENING  
FOR OESOPHAGEAL VARRICES ?**

## WOULD YOU PERFORM SCREENING FOR OESOPHAGEAL VARRICES ?



**LSM = 27 KPA  
PLT = 175 00  
HVPg = 18 mmHG**



Gr II OV



- Band Ligation?
- Switch to Propranolol?
- Continue Carvedilol?



# PRIMARY PROPHYLAXIS OF VARICEAL BLEEDING

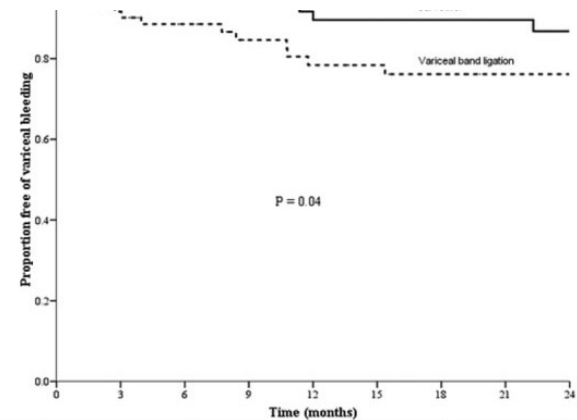
## BAVENO VI

*Patients with medium-large varices (unchanged)*

- Either NSBB or endoscopic band ligation is recommended for the prevention of the first variceal bleeding of medium or large varices (1a;A).
- The choice of treatment should be based on local resources and expertise, patient preference and characteristics, contraindications and adverse events (5;D).

On intention-to-treat analysis, carvedilol had lower rates of the first variceal bleed (10% versus 23%; relative hazard 0.41; 95% confidence interval 0.19-0.96 [P 0.04]),

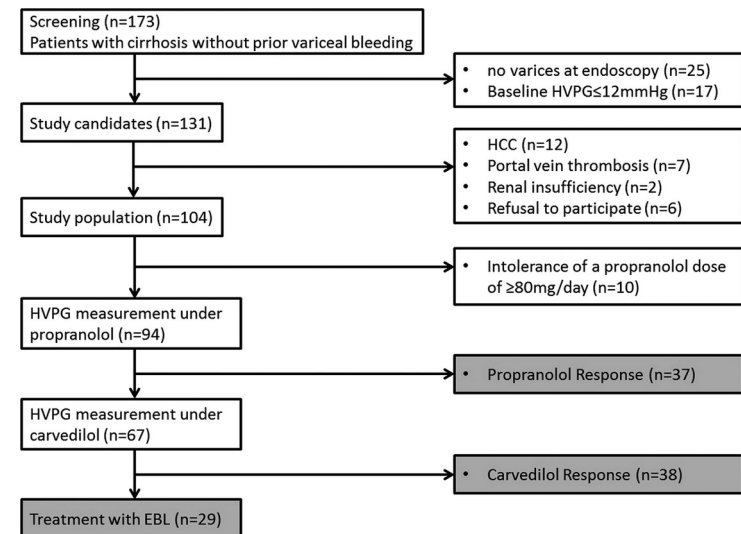
RCT : 152 cirrhotic patients with gr II EV → Carvedilol 12.5 mg/day or VBL



| Time (months)  | 0  | 6  | 12 | 18 | 24 |
|----------------|----|----|----|----|----|
| Carvedilol (n) | 77 | 57 | 43 | 35 | 29 |
| VBL (n)        | 75 | 51 | 37 | 32 | 27 |

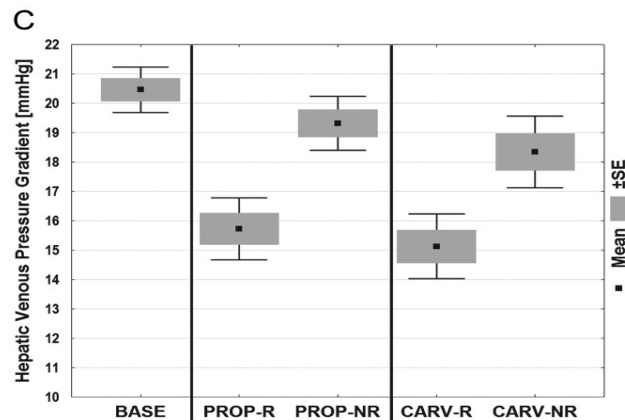
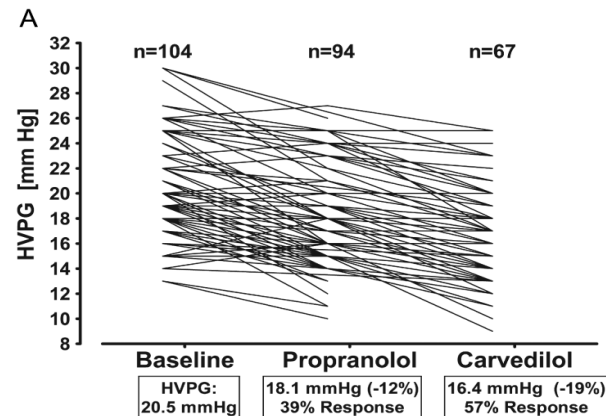
D 1.0

# Carvedilol leads to a significantly greater decrease in HVPG than propranolol



|                | PROP | CARV | EBL | P     |
|----------------|------|------|-----|-------|
| Bleeding rate  | 11%  | 5%   | 25% | 0.042 |
| Hepatic decomp | 38%  | 26%  | 55% | 0.07  |
| Mortality      | 14%  | 11%  | 31% | 0.045 |

Reiberger, Gut 2013





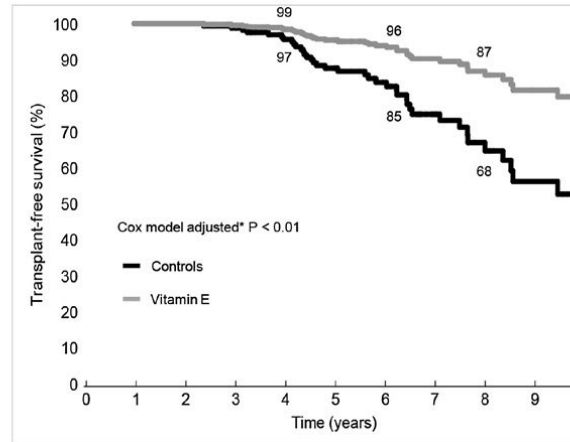
## TREATMENT :

METFORMIN 1000 mg,  
IRBESARTAN/HCT 150/12.5 mg,  
LTHYROXIN 75 µg

LIRAGLUTIDE  
ATORVASTATIN 10 MG/D  
PREVISCAN  
CARVEDILOL 12.5 MG/D  
VITAMIN E 500 IUx2/D

236 pts with F3F4 NASH  
FU – 5.6 years  
Vitamin E 800 IU/D ≥ 2 years

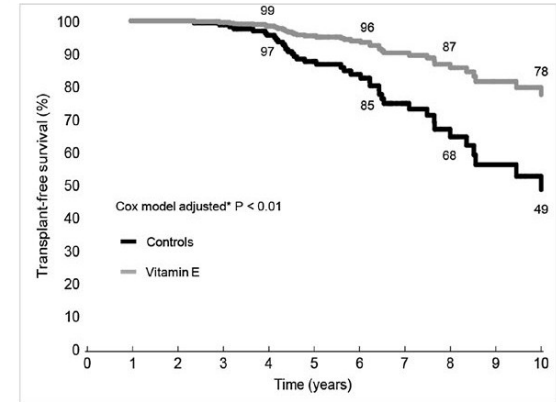
A



No. at risk  
Vitamin E  
Controls

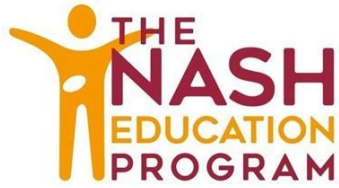
|    |    |    |    |    |    |    |    |    |    |   |
|----|----|----|----|----|----|----|----|----|----|---|
| 90 | 89 | 84 | 77 | 67 | 55 | 38 | 21 | 13 | 10 | 8 |
| 90 | 90 | 89 | 85 | 76 | 55 | 41 | 29 | 19 | 12 | 8 |

A



No. at risk  
Vitamin E  
Controls

|    |    |    |    |    |    |    |    |    |    |   |
|----|----|----|----|----|----|----|----|----|----|---|
| 90 | 89 | 84 | 77 | 67 | 55 | 38 | 21 | 13 | 10 | 8 |
| 90 | 90 | 89 | 85 | 76 | 55 | 41 | 29 | 19 | 12 | 8 |



# Basic Patient Problems in NAFLD, NASH



- Who is my doctor?
  - Should I consult hepatologists?
  - Nutritionist?
  - Gastroenterologist?
- What drugs I need to take?
- Did I do it to myself?
- You did it to your self!
- Where can I get more info?
- Where can I turn for help?

➤ **CONFUSION**

➤ **LACK OF CHOICES**

➤ **SELF-STIGMATIZATION**

➤ **STIGMATIZATION**

➤ **LACK OF RELIABLE INFORMATIONS**

➤ **LACK OF PATIENT ORGANIZATIONS**

# NASH CLINIC – MULTIDISCIPLINARY APPROACH

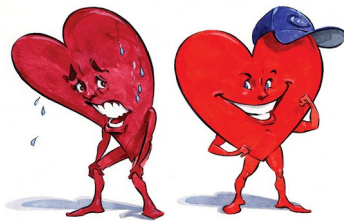
## PHRTAMACOLOGIC THERAPY/ CLINICAL TRIALS



## CARDIAC STRESS TESTING & ADAPTED PHYSICAL ACTIVITY COUNSELING

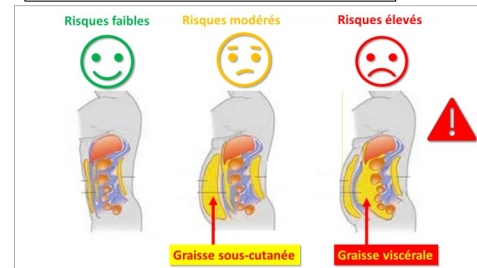


## CV RISK EVALUATION

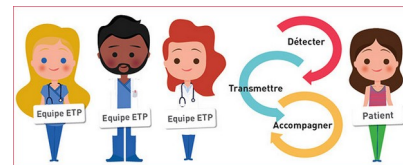


## NUTRION COUNSELING

## METABOLIC RISK



## LIVER DAMAGE



## PATIENT EDUCATION